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CENTRAL RESPIRATORY EFFECTS OF CARBON DIOXIDE, AND CAROTID SINUS NERVE AND MUSCLE AFFERENTS

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SUMMARY

1. In anaesthetized and paralysed cats, artificially ventilated and with the vagi and carotid sinus nerves cut, the effects of (*a*) changing end-tidal CO_2, (*b*) stimulation of carotid sinus nerves, and (*c*) squeezing the calf muscles, on neural respiratory output have been studied.

2. The peak value of integrated phrenic activity, which is the neural equivalent of tidal volume (VT_n), the rate of rise of integrated phrenic activity (*Slope*), inspiratory duration (T_I), expiratory duration (T_E), and total cycle length (T_{tot}) were measured. It was found that *Slope*-VT_n, VT_n-T_{tot} and VT_n-T_E relationships were similar whether respiration was stimulated by carotid sinus nerve stimulation or by increasing end-tidal CO_2. However, when respiration was stimulated by squeezing the calf muscles, a given *Slope* was associated with a smaller VT_n and a given VT_n was associated with smaller T_{tot} and T_E values than obtained with the other two inputs.

3. It is concluded that these results are compatible with the hypotheses that (1) inputs from central and peripheral chemoreceptors have similar actions at various sites in the respiratory centre complex, and (2) afferents activated by squeezing the limb muscles have additional facilitatory actions on mechanisms terminating inspiration and expiration.

INTRODUCTION

There have been a number of studies comparing the effects of hypoxia and hypercapnia on the various parameters of respiratory activity, with a view to gain information on the effects of central and peripheral chemoreceptors. However, the results are conflicting. Rosenstein, McCarthy & Borison (1973) and Widdicombe & Winning (1974) found similar patterns of respiratory activity for hypoxic and hypercapnic stimuli with vagi cut as well as intact. However, Miserocchi (1976) reported that peripheral chemoreceptor activity had no effect on the central respiratory rhythm whereas hypercapnia increased both frequency and tidal volume. On the other hand, Ledlie, Kelsen, Altose & Cherniak (1977) reported that hypoxia caused a greater increase in frequency of breathing than did hypercapnia.

Thus it is clear that there is no definitive information regarding the similarities or otherwise of the respiratory effects of central and peripheral chemoreceptors. Such

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information is important for a complete understanding of the respiratory control mechanism. The present work was undertaken to study the effects of increasing inputs from central chemoreceptors and peripheral chemoreceptor afferents on neural respiratory output. The method used for increasing the input from peripheral chemoreceptor afferents avoids the complications that central effects of hypoxia (Miller & Tenney, 1975*a*, *b*; St John and Wang, 1977) may introduce. We have also studied the effect of increased input from limb muscle afferents which are known to stimulate respiration (Senapati, 1966; Eldridge, 1974), and which may conceivably have a role in the regulation of respiration during muscular exercise (McCloskey & Mitchell, 1972).

METHODS

These experiments were done in twelve cats anaesthetized with chloralose (40 mg/kg) and urethane (250 mg/kg) given intravenously under preliminary ether anaesthesia. Trachea was cannulated and the femoral artery was catheterized for recording of arterial pressure. The vago-sympathetic trunks were cut in the neck and both carotid sinus nerves were cut or crushed near the carotid bodies. One of the carotid sinus nerves was put on platinum electrodes for subsequent stimulation. The fifth cervical phrenic root on one side was exposed and cut. The activity of the central end was recorded with platinum electrodes that led into a differential pre-amplifier with a band pass 100–3000 Hz. Both nerves were covered with pools of mineral oil. Airway CO_2 was monitored continuously with an infra-red analyser (Beckman LB-2). The animal was paralysed with gallamine triethiodide given intravenously and was ventilated with 100 % O_2 by means of a respirator that delivered a constant preset volume of gas during each inflation. Gallamine triethiodide in suitable doses was repeated when necessary. The rectal temperature of the cat was maintained at $37{\cdot}5 \pm 1$ °C by heating. However, the temperature during any set of procedures was not allowed to vary more than 0·5 °C. Phrenic activity was integrated over 0·1 sec periods using the method described by Eldridge (1971).

Experimental protocol

The following parameters of neural respiratory output were measured. (1) peak value of integrated phrenic activity, which is the neural equivalent of tidal volume (VT_n) and (2) rate of rise of integrated phrenic activity (*Slope*), which has been proposed to be a measure of drive to the inspiratory output neurones (Bradley, von Euler, Martilla & Roos, 1975). It was found that in the preparations used in this study phrenic activity increased linearly with time through a large part of inspiration. *Slopes* were therefore determined by the method of linear regression. The portion of inspiratory time to be used for determining *Slope* by this method could be easily ascertained by looking at the phrenic integral and was usually 0·6–0·9 sec duration. Out of a total of 2839 cycles analysed in the course of this study, the values of correlation coefficient in all but fifteen cycles were $\geqq 0{\cdot}9$. These fifteen cycles were excluded from analysis when determining the average values of different variables, (3) inspiratory time (T_I); (4) expiratory time (T_E), and (5) total length of the cycle (T_{tot}).

All these measurements are shown in Fig. 1, which also shows VT_n/T_I for comparison with the *Slope* as measured in this study. When there is a flattening of the phrenic integrated activity towards the end of inspiration (terminal inhibition, Younes, Baker & Remmers, 1977), as in this figure, the value of VT_n/T_I is affected by the activity of the inspiration terminating mechanism. The values of these variables were determined using a computer; the value of T_E was determined by subtracting T_I from T_{tot}. For each input studied the steady state values of the different variables were averaged for eight or more cycles and these average values were used for analysis. The volume of inflation for artificial ventilation was kept constant throughout.

Input from peripheral chemoreceptor afferents was increased by electrical stimulation of one carotid sinus nerve with stimulus trains at a frequency of 25 Hz, 0·5 msec pulse duration, and isolated from ground. The amount of input from this source was changed by varying the stimulation voltage. The size of the stimulus artifact picked up by the phrenic recording electrodes, even at the highest intensities of stimulation used, was insignificant and it was therefore not

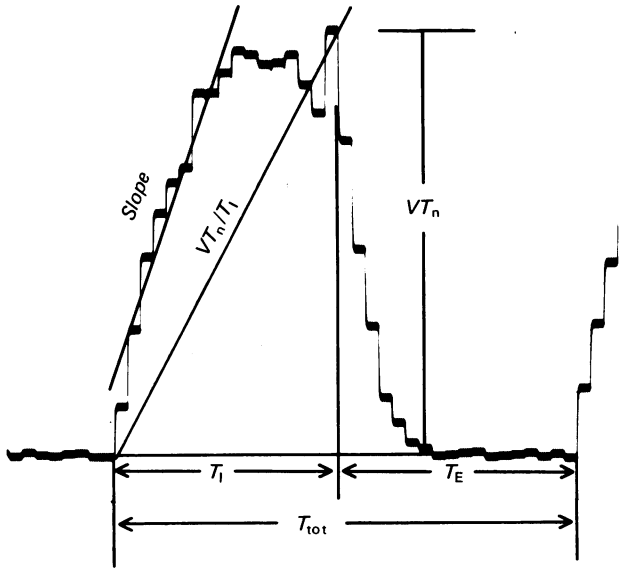

Fig. 1. One complete cycle of integrated phrenic activity showing the various parameters of neural respiratory output used in this study. The line marked *Slope* has been drawn by eye in this Figure but the values of *Slope* used in analysis of results were determined by regression. Also shown in this Figure is the line marked VT_n/T_I, the slope of which gives the average rate of rise of integrated activity through inspiration.

necessary to subtract it from the integrated value of phrenic nerve activity. For all levels of carotid sinus nerve afferent input in any particular animal, the end-tidal pCO_2 was kept constant. This was done by using an electronic servo-controller the output of which varied as a function of end-tidal pCO_2 and controlled the frequency of the respiratory pump (Smith, Mercer & Eldridge, 1978). The end-tidal pCO_2 in all the animals, however was not the same; the range was 24–36 torr. Phrenic activity was analysed after the peak integrated value (VT_n) had reached a steady level. The stimulation at each level of intensity usually lasted 1·5–2 min. Six to twelve levels of input were studied in each animal. It is recognized that electrical stimulation of carotid sinus nerve stimulates baroreceptor as well as chemoreceptor fibres. However, as discussed later (see Discussion), the admixture of baroreceptor input should not affect the results of this study.

Central chemoreceptor input was increased by raising the end-tidal pCO_2. For this purpose dead spaces of different sizes were introduced in the ventilatory circuit. Since the animal was ventilated with 100 % O_2, the reduction of alveolar ventilation produced by increasing the dead space increased end-tidal pCO_2 but would have left arterial pO_2 high. The arterial pO_2 levels were not measured. The range of lower levels of end-tidal pCO_2 in all the animals was 25–36 torr, and that of upper levels 52–70 torr. The effects of four to nine levels of end-tidal pCO_2 were studied in each animal. Each level of end-tidal pCO_2 was maintained for 6–7 min and the phrenic nerve activity was analysed at the end of this period.

Limb muscle afferents were stimulated by squeezing the calf muscles or by marked dorsiflexion of the ankles, keeping the knees extended. Both these methods of activating the limb muscle afferents gave similar results, and either one was used according to convenience. Stretch of calf muscles by pulling on their tendons produces a much smaller increase in ventilation than squeezing the muscles (Senapati, 1966; also observations during the course of this study). However, since we found that both methods produce similar changes in neural respiratory output, it is probable that they activate the same set of receptors.

As it was not possible to grade accurately the input from leg muscles by the manual procedure employed, the effects of varying intensities of input from this source were not studied. However the effects of muscle afferent input were studied by squeezing the calf muscles at three to seven different levels of end-tidal pCO_2; in eight of the cats, the effects of more than four levels were

studied. The ranges of lower and upper levels of end-tidal pCO_2 were the same as those for central chemoreceptor input. As in the case of input from central chemoreceptors and carotid sinus nerve afferents phrenic nerve activity was analysed when VT_n values had reached a steady level. The duration of each activation of limb muscle afferents was 1–1·5 min.

The sequence in which the various drives were studied was usually: carotid sinus nerve afferent input, central chemoreceptor and 'central chemoreceptor + calf muscle afferent' input. At a particular level of end-tidal pCO_2 after the effects of central chemoreceptors had been studied, calf muscle afferents were activated and their effects were studied. In two cats, the central chemoreceptor and calf muscle afferent inputs were studied before the carotid sinus nerve afferent input.

RESULTS

Increased input from the carotid sinus nerve afferents as well as central chemoreceptors increased the rate of rise (*Slope*) as well as peak value (VT_n) of integrated phrenic activity. An example of this is shown in Fig. 2. Von Euler, Martilla, Remmers & Trippenbach (1976) have reported similar results in cats for increasing levels of CO_2. However, since the carotid sinus nerves in their animals were intact, their results were probably due to a combination of increased input from central as well as peripheral chemoreceptors.

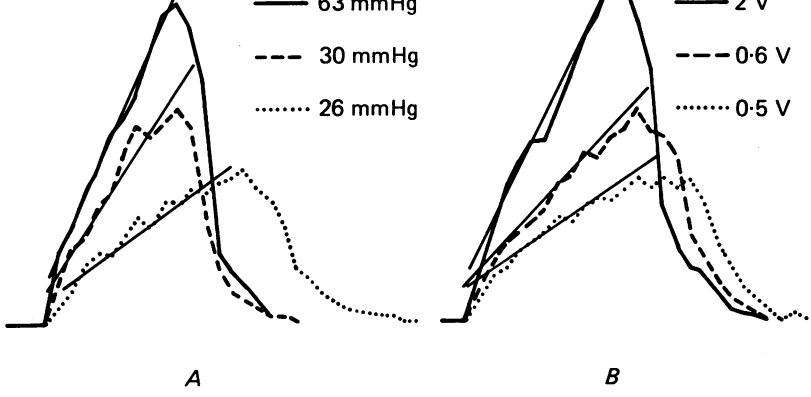

Fig. 2. Cycles of integrated phrenic activity at different levels of end-tidal pCO_2 (*A*) and at different intensities of carotid sinus nerve stimulation (*B*) from one cat. Each cycle has been constructed by plotting the activity at sequential 0·1 sec intervals from photographic records like the one in Fig. 1. The lines indicating slopes have been drawn by eye.

Comparing the effects of the three inputs used in this study, it was found that for a given VT_n, input from limb muscle afferents gave a bigger *Slope* than did the other two (Fig. 3). In this Figure, cycles of integrated phrenic activity during each of the three inputs from one animal, chosen so that the VT_n values for the three are nearly the same, have been superimposed. For similar VT_ns, the *Slopes* for central chemoreceptor and carotid sinus nerve inputs are similar but the *Slope* for muscle afferents is greater.

In subsequent analyses the average values of each variable obtained from eight or more (usually ten) cycles were determined for each steady-state condition studied. To analyse the actions of the three inputs on the respiratory control complex in as great

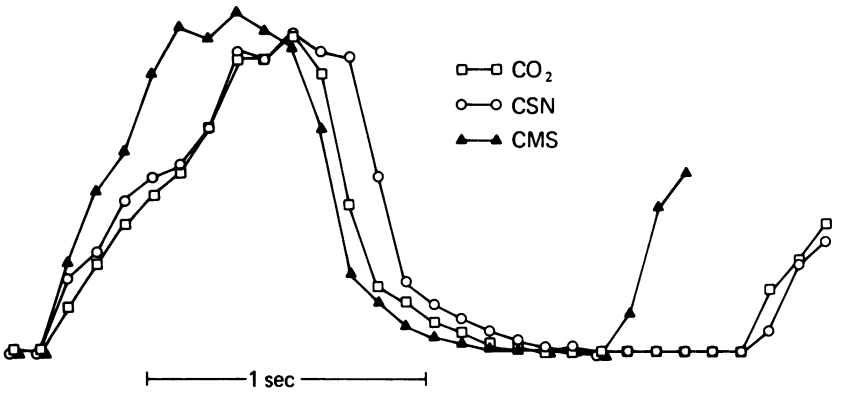

Fig. 3. Three complete cycles of integrated phrenic activity from one cat, plotted in the same manner as Fig. 2, and selected to have the same neural tidal output (VT_n). □—□, activity at a certain level of end-tidal pCO_2; ○—○, during stimulation of carotid sinus nerve (CSN); ▲—▲ during calf muscle squeeze (CMS).

a detail as possible we studied the nature of the following relationships: (1) rate of rise of phrenic integral (*Slope*), and neural tidal volume (VT_n), (2) VT_n and cycle length (T_{tot}), (3) VT_n and expiratory time (T_E), and (4) inspiratory time (T_I) and expiratory time (T_E). VT_n and *Slope* were expressed as a percentage of the maximum values obtained in a particular animal during the whole course of the experiment.

Slope–VT_n relationship. For central chemoreceptor and carotid sinus nerve inputs, similar *Slopes* were associated with similar VT_n values in all animals (Fig. 4). The relationship between *Slope* and VT_n was linear; in all but one cat the correlation coefficients (r) were $> 0{\cdot}97$ (the values of r for the remaining cat were $> 0{\cdot}92$). Similar relationship between these two variables, obtained from diaphragmatic e.m.g. in man is implied in the results reported by Lopata, Evanich & Lourenço (1977); they found that both peak value and peak value/T_I were linearly related to pCO_2.

In the case of input from limb muscle afferents (studied in ten animals), a given *Slope* was always associated with a smaller VT_n than for the central chemoreceptor and carotid sinus nerve inputs and the relationship between *Slope* and VT_n was not always linear (Fig. 4). However, it should be noted that in this case both central chemoreceptor and muscle afferent inputs were changed.

VT_n–T_{tot} and VT_n–T_E relationships. In six animals VT_n–T_{tot} and VT_n–T_E curves for the central chemoreceptor and carotid sinus nerve inputs were very close to each other, but the curves for muscle afferent input were clearly below the other two in all ten animals. Fig. 5 shows these curves for one of these six animals. In two of the remaining animals the carotid sinus nerve curves were higher than the CO_2 curves, but in another the CO_2 curves were higher than the carotid sinus nerve curves. In the three remaining cats the CO_2 and carotid sinus nerve curves diverged in the range of higher values of VT_n, the CO_2 curves being higher than the carotid sinus nerve curves in this range. Fig. 6 shows the VT_n–T_{tot} curves for one of these three cats.

In these preparations, the manner in which cycle length (T_{tot}) changed with increasing drive to respiration varied in different animals. In some T_{tot} increased with increasing VT_n (Figs. 5 and 6), in some it remained practically unchanged, and in

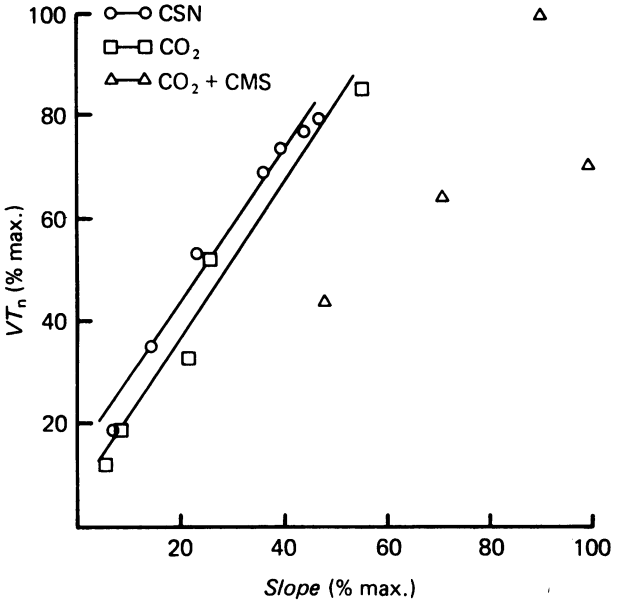

Fig. 4. Relationship between *Slope* and VT_n in one cat. ○—○, carotid sinus nerve stimulation at different intensities; □—□, different levels of end-tidal pCO_2; △—△ squeezing the calf muscles (CMS) at different levels of end-tidal pCO_2. Each point represents the mean of eight to ten cycles during each steady-state condition. Both *Slope* and VT_n are expressed as a percentage of the maximum value of the parameter obtained in the cat. The lines are drawn by eye (cat 148).

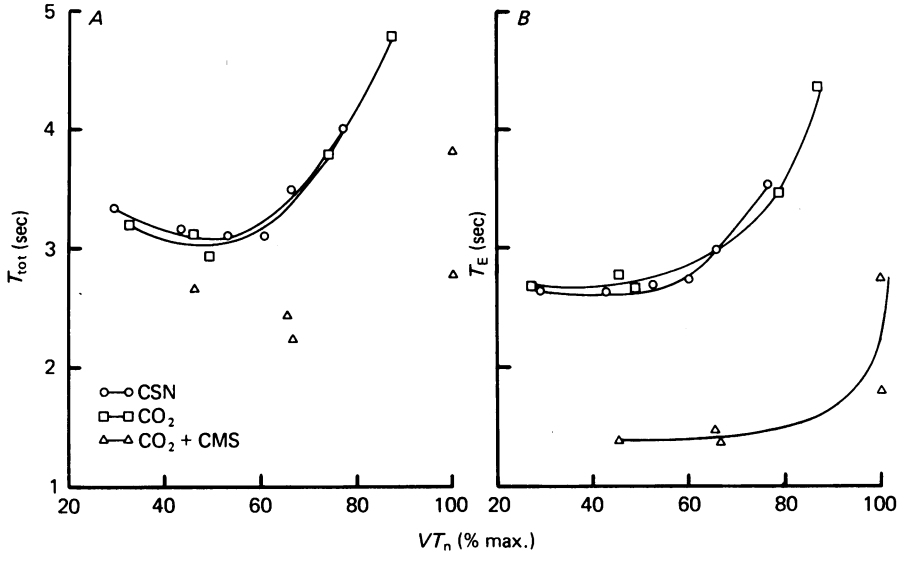

Fig. 5. Relationship between VT_n (espressed as a percentage of the maximum value obtained in the cat) and T_{tot} (*A*) and VT_n and T_E (*B*) in one cat. ○—○, carotid sinus nerve stimulation at different intensities; □—□, different levels of end-tidal pCO_2; △—△, squeezing the calf muscles (CMS) at different end-tidal pCO_2 levels. Each point represents the mean of eight to ten cycles during each steady-state condition (cat 147).

others it decreased. Fig. 7 shows VT_n–T_{tot} curves from an animal in which T_{tot} decreased as VT_n increased. There is considerable scatter of points for the CO_2 curve,

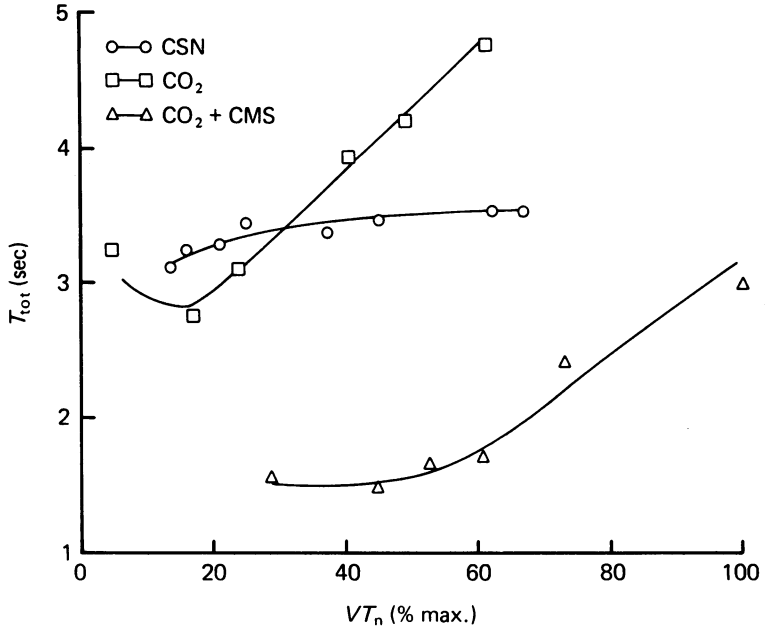

Fig. 6. Relationship between VT_n and T_{tot} in cat 156. Symbols and method of construction same as in Fig. 5.

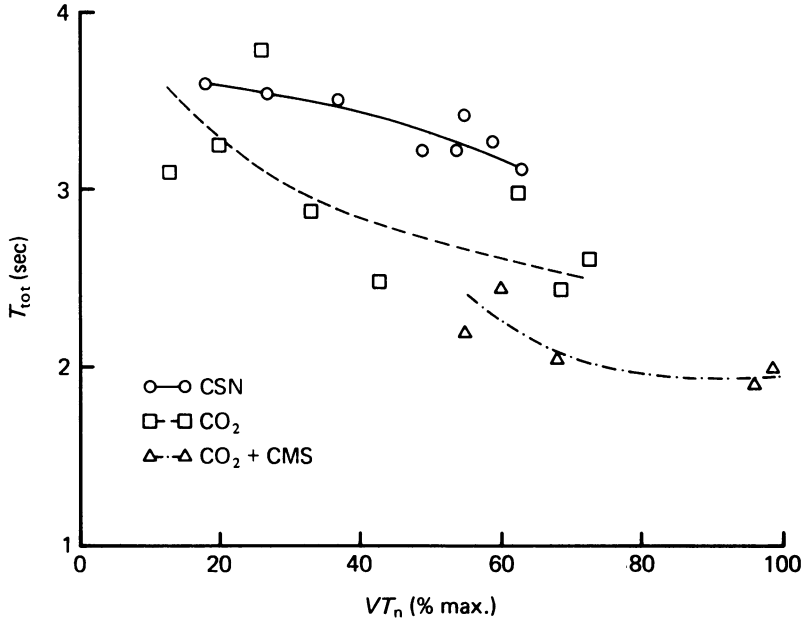

Fig. 7. Relationship between VT_n and T_{tot} in cat 158. T_{tot} decreased as VT_n increased in this animal. Symbols and method of construction same as in Fig. 5.

but for each input, the values of T_{tot} at the right hand end of the curve are smaller than those at the left hand end.

In ten cats, changes in respiratory drive produced qualitatively similar directional changes in T_{tot} and T_E. In one cat, T_{tot} decreased as VT_n increased but there was hardly any change in T_E. In the remaining cat, for the chemoreceptor drives, T_{tot} decreased as VT_n increased, but T_E changed very little; for muscle afferent input both T_{tot} and T_E increased as VT_n increased.

For each input, the mean T_{tot} values for all the animals studied were determined for 10 % VT_n intervals using the actually determined values for calculating the mean. Fig. 8 shows the relationship between VT_n and mean T_{tot} for the three inputs. There is no significant difference between the carotid sinus nerve and CO_2 curves at any point, as determined by the two tailed t test for unpaired group data ($P > 0{\cdot}22$ at every point). The muscle curve is significantly different from the CO_2 curve at every point ($P \leqq 0{\cdot}016$ at every point except the 30–40 % VT_n interval where $P = 0{\cdot}053$). The difference between the muscle and carotid sinus nerve curves is statistically significant at all points up to 90 % VT_n, ($P \leqq 0{\cdot}007$ at all points up to 80 % VT_n and $P = 0{\cdot}047$ in the 80–90 % interval) but not in the 90–100 % interval where $P = 0{\cdot}16$. Thus it is clear that, compared to the CO_2 and carotid sinus nerve inputs, muscle afferents activated by squeezing the limb muscles give rise to a higher respiratory rate for a given VT_n value.

T_I–T_E relationship. In these preparations there was no consistent relationship

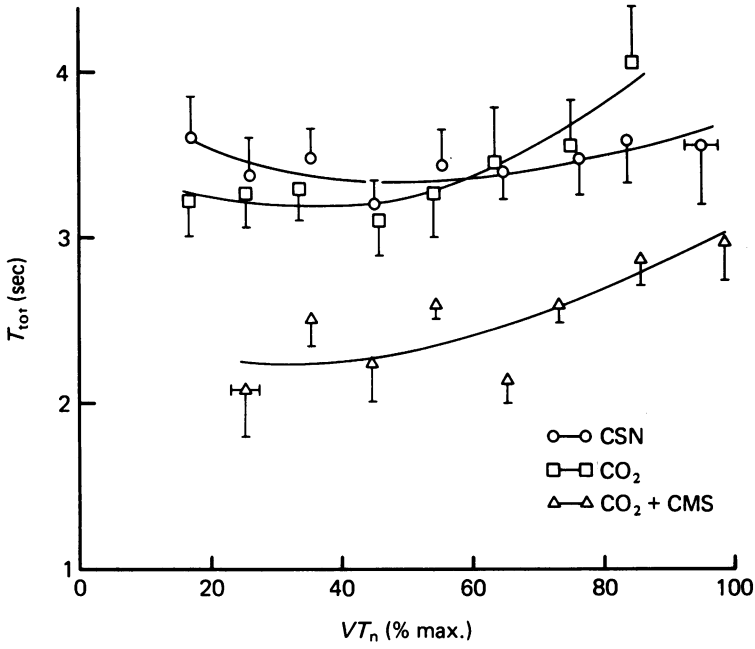

Fig. 8. The relationship between VT_n and mean T_{tot} for the three types of inputs studied. Each point represents the average value of T_{tot} for all the animals studied. The vertical and horizontal bars represent one S.E. mean. The S.E. mean for VT_n are shown only for those points where they extended beyond the sizes of the symbols. Details in text.

between T_I and T_E. In four cats T_I and T_E changed in the same direction; in two cats T_I remained practically unchanged while T_E increased; in one cat T_I changed while T_E remained practically unchanged; in four cats, for part of the range of observations T_I remained practically unchanged when T_E changed; for the remainder, in one cat T_I and T_E changed in the same direction, and in the other three in opposite directions. In one cat T_I and T_E changed in opposite directions for one of the drives and in the same direction for the other two drives.

In addition to influencing neural respiratory activity, muscle squeezing always caused a rise in arterial pressure. In the case of carotid sinus nerve stimulation, increasing the intensity of stimulation had variable effects on blood pressure. In 67 % of the runs there was no change in arterial pressure, in 19 % there was a small increase and in 14 % there was a small decrease. Increasing the end-tidal CO_2 usually caused a slight to moderate decrease in blood pressure.

DISCUSSION

The method of increasing the input from peripheral chemoreceptors by electrical stimulation of carotid sinus nerve, while eliminating the central effects of hypoxia, introduces a different complication, an admixture of input from baroreceptors. However, since Grunstein, Derenne & Milic-Emili (1975) showed that baroreceptor activity depresses respiration without altering the relationship between various parameters of respiratory activity, the admixture of baroreceptor input with chemoreceptor input in this study, should not affect the relationships that have been used in analyses. Because of this fortunate circumstance, electrical stimulation of carotid sinus nerve could be used to study the effects of peripheral chemoreceptor input on respiration without the complicating effects of hypoxia, referred to earlier.

The results reported in this study pertain to the effects of the three inputs on the respiratory centre complex without any modifications due to alterations in other afferent inputs (except for the admixture of baroreceptor input which is discussed above). Since the vagi and carotid sinus nerves were cut, arterial pCO_2 acted only on the respiratory centre complex. It is important to bear this in mind, as in a preparation with the vagi and the carotid sinus nerves intact, CO_2 acts on central as well as peripheral chemoreceptors, and also has some effect on the activity of pulmonary stretch receptors (Mustafa & Purves, 1972; Sant'Ambrogio, Miserocchi & Mortola, 1974). The input from the intercostal muscle afferents which has been shown to have central respiratory effects (Remmers & Martilla, 1975) was intact in our preparations. However, since the animals were paralysed and artificially ventilated with a constant inflation volume throughout, the input from this source must have been rather small and, what is more important, remained constant. This is further borne out by the fact that phrenic activity did not vary with the phases of the respiratory pump. Possible effects of limb muscle afferents at the spinal level or direct effects of CO_2 on phrenic motoneurones (Gill & Kuno, 1963) cannot be ruled out. The direct effects of CO_2, however, do not seem to affect significantly the use of integrated phrenic activity as an index of central inspiratory activity (von Euler & Trippenbach, 1976; von Euler, 1977).

Similar *Slope*–VT_n relationships for central and peripheral chemoreceptor inputs

imply that for equal drives to the inspiration generating mechanism from these two sources, effects on the mechanism terminating inspiration are similar. This conclusion may not be valid if one input consistently produced more rounding of the phrenic integral towards the end of inspiration, than the other. However we did not observe any such selective effect. In most preparations the VT_n–T_{tot} and VT_n–T_E relationships for these two inputs were either similar (six cats) or the differences were not in a consistent direction (three cats). The mean VT_n–T_{tot} relationships for the population were not significantly different at any point (Fig. 8). Similar VT_n–T_E and VT_n–T_{tot} relationships imply that for similar cyclic outputs from the inspiration generating mechanism, effects on the mechanisms terminating expiration and inspiration are similar. These results are compatible with the hypothesis that central and peripheral chemoreceptor inputs have similar actions at various sites in the respiratory control complex.

There is the theoretical possibility that even though the interaction between central chemoreceptor input and baroreceptor input to the respiratory centre is such that it results in a simple depression of ventilation (Grunstein *et al.* 1975, referred to earlier), the interaction between baroreceptor and peripheral chemoreceptor afferents may be more complex. If this is the case then the only way the present results can be explained is that the effects of peripheral chemoreceptor input on mechanisms terminating inspiration and expiration are different from those of central chemoreceptor input, but that the varying input from baroreceptor afferents cancels out these differences at all levels of drive, so that the mixed input with varying contributions from each component produces effects which are indistinguishable from those of central chemoreceptors. This seems a much more unlikely possibility than the one that the interaction between peripheral chemoreceptor and baroreceptor inputs is simple like the one reported by Grunstein *et al.* for central chemoreceptors and baroreceptors.

However, in three out of twelve cats the VT_n–T_{tot} and VT_n–T_E curves for the two chemoreceptor inputs diverged in the range of higher VT_n values, the CO_2 curves being higher than the carotid sinus nerve curves (Fig. 6); the central chemoreceptor input thus giving a lower respiratory rate than the peripheral chemoreceptor input for equivalent VT_n values. This may be due to a direct action of CO_2/H^+ on some parts of the respiratory centre complex besides its action on the central chemoreceptors, for CO_2 has been shown to have direct depressant actions on central neurones involved in respiratory control (Gill & Kuno, 1963; Mitchell & Herbert, 1974). However, the alternate possibility that there is a difference in the action of central and peripheral chemoreceptors on the mechanism terminating expiration cannot be ruled out entirely.

Our conclusions that central and peripheral chemoreceptors most probably have similar actions at various sites in the respiratory control mechanism seem to be in conflict with the conclusions of St John and associates (St John, Bond & Pasley, 1975; St John & Wang, 1976). These authors reported that lesions of the pneumotaxic centre reduced the ventilatory response to CO_2, leaving the ventilatory response to hypoxia unchanged, and concluded that the input from central and peripheral chemoreceptors is integrated differently by the brain-stem structures. However, one section of their results does not fit in with this conclusion: when they maintained the end-tidal pCO_2 of their animals at 40 mm Hg, which was the level after lesions of the

pneumotaxic centre, and consequently the lowest level for starting the hypercapnic stimulation, the response to hypoxic stimulation was also reduced. Moreover, von Euler *et al.* (1976) found that apneustic promoting lesions of the medial parabrachial nucleus do not necessarily reduce the CO_2 responsiveness of the respiratory control mechanism. They suggested that it is possible that other structures in the vicinity of the medial parabrachial nucleus may exert a gain controlling effect on the sensitivity of central chemoreceptors and that this may account for the different results obtained by St John and associates.

That afferents stimulated by squeezing the limb muscles increase respiratory frequency more than chemoreceptor inputs is also indicated by analysis of the data of Mizumura & Kumazawa (1976). (These authors were not concerned with this aspect and hence did not comment on it.) They had stimulated muscle afferents by intra-arterial injections of hypertonic saline, a procedure that stimulates the same afferents that are activated by squeezing the muscles (Paintal, 1960).

Our results relating to muscle afferent input suggests that these afferents in addition to increasing the drive to respiration, have additional more direct facilitatory action on the mechanism or mechanisms terminating inspiration and expiration. Such a facilitatory action on the inspiration terminating mechanism would account for smaller VT_n values for equivalent *Slopes*, compared with the values obtained with chemoreceptor inputs. The effect on T_E may be secondary to the effect on the mechanism terminating inspiration, or there may be an additional facilitatory action on the expiration terminating mechanism. The latter is more likely as we did not find a consistent relationship between T_I and T_E in these preparations; increase in T_E could be associated with practically no change, increase or even a decrease in T_I (see Results). Iscoe & Polosa (1976) reached a similar conclusion. Studying the effects of electrical stimulation of muscle nerves during different phases of the respiratory cycle on the durations of T_I and T_E, they stated that some of their results suggest that these afferents have a direct facilitatory action on the inspiratory inhibitory and expiratory inhibitory loops.

Nothing is known regarding the physiological role of muscle afferents that can be activated by squeezing the limb muscles. However, the results of McCloskey & Mitchell (1972), who found that muscle afferents that produce reflex hyperpnea and rise in blood pressure during muscular exercise, belong to the population with fibre diameters in a range smaller than 'group 11', taken together with Paintal's results that a significant proportion of afferents activated by squeezing the muscle are also activated during muscular contraction (Paintal, 1960) suggest that some of these afferents may have a role in the hyperpnea of muscular exercise. Our results that the stimulation of these afferents gives different *Slope*–VT_n, VT_n–T_{tot}, and VT_n–T_E relationships from those given by the chemoreceptor inputs (peripheral as well as central) provide a method for resolving this point. Phillipson, Hickey, Bainten & Nadel (1970) working with conscious dogs, and Lahiri, Mei & Kao (1975) working with anaesthetized dogs reported that whereas vagotomy markedly impaired the rate response of ventilation to chemical stimuli, the rate response of ventilation during exercise was much less affected. However, since the temperatures of their animals were not controlled, and rise in temperature specifically increases frequency of respiration, these results may have been due to rise in body temperature during

exercise. Whether these muscle afferents have a role in the hyperpnea of muscle exercise, therefore still remains to be determined.

Since the submission of this manuscript, St John (1979) has reported that in decerebrate vagotomized cats: (1) respiratory frequency may increase, decrease or remain practically unchanged as respiratory drive is increased, (2) T_I and T_E may change in the same direction, opposite direction, or one may change while the other remains practically unchanged (Fig. 6 of St John's paper). These results are similar to those reported in this study.

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